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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,062	01/21/2006	Anita Mehta	RLL-283US	1323

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EXAMINER	
SOLOLA, TAOFIQ A	
ART UNIT	**PAPER NUMBER**
1625	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,062	MEHTA ET AL.	
	Examiner	Art Unit	
	Taofiq A. Solola	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 1-18 are pending in this application.

Claim Rejections - 35 USC § 112

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims lack adequate support in the specification. The terms "solvates" "polymorphs", "metabolites" are not defined in the specification so as to ascertain the structures of the compounds that are included and/or excluded by the term. Specifically, the specification fails to disclose the number of moles of water that would form the solvates, the crystalline structures of the polymorphs and how they are formed, and the structures of the metabolites and how they are formed in and/or outside the body. In patent examination, it is essential for claims to be precise, clear, correct, and unambiguous. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989). By deleting the terms the rejection would be overcome.

The term "hydrocarbon group" (e.g. claim 1, line 19) is not defined in the specification so as to ascertain the structures of compounds that included and/or excluded by the term. The term embraces the entire textbook of organic chemistry. There is no support for such in the specification. There is no conclusive evidence that such molecules are enabled by the process disclosed in the specification and if made there is no evidence such compounds would have the asserted utility. The only "hydrocarbon group" at position R7 made in all the examples is methyl. The term embraces far more complex molecules than are made in the examples. Steric hindrance and/or interference would more than likely be a problem and the specification fails to disclose how such problem could be resolved. Applicant must show possession of the

invention by describing it with all the claimed limitations. *Lookwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed Cir. 1997). By replacing the term with methyl the rejection would be overcome.

Claim 15 recites a temperature range of "from about 0-140° C. Such range is not supported in the specification. All the examples are made between 0 to room temperature. By deleting the claims the rejection would be overcome. See *Lookwood,* supra.

Claims 5-6 and 9 are drawn to all respiratory, urinary and gastrointestinal (GI) diseases mediated by muscarinic receptors. This is not a practical utility under the US patent practice. To ascertain the practical utility, one must read the specification into the claims contrary to several precedent decisions by US courts and Official practice. Even then, the claims would become duplicates of 7-8, 10. Under the US patent practice duplicates or substantial duplicates claims cannot be in the same application. The claims are attempts by applicant to claim treatment/prevention (prophylaxis) of all respiratory, urinary and gastrointestinal (GI) diseases known today and that may be discovered in the future, mediated by muscarinic receptors. They are reach-through claims and are no longer patentable under the US patent practice. A claim must stand alone to define the invention, and incorporation into the claims by reference to the specification or an external source is not permitted. Ex parte Fressola, 27 USPQ 2d 1608, BdPatApp & Inter. (1993). By deleting the claims the rejection would be overcome.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for methyl at R7, for treating some of the listed diseases does not reasonably provide enablement for all possible hydrocarbon groups, for preventing or treating all respiratory, urinary and gastrointestinal (GI) diseases mediated by muscarinic receptors. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

"'In the context of determining whether sufficient "utility as a drug, medicant, and the like in human therapy" has been alleged, It is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the [compounds and the utilities] as obviously correct." *In re Jolles*, 628 F.2d 1327, 1332 (Fed. Cir. 1980), citing *In re Novak*, 306 F.2d 924 (CCPA 1962); see 340 F.2d 974, 977-78 (CCPA 1965).

"A specification disclosure which contains a teaching of the manner and process of making and using the invention . . . must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), Id. at 1566, quoting *Marzocchi*, 439 F.2d 220, 223 (CCPA 1971); *Fiers v. Revel,* 984 F.2d 1164, 1171-72 (Fed. Cir. 1993), quoting *Marzocchi*, 439 F.2d at 223; see also *Armbruster*, 512 F.2d 676, 677 (CCPA 1975); *Knowlton*, 500 F.2d 566, 571 (CCPA 1974); *Bowen*, 492 F.2d 859 (CCPA 1974); *Hawkins*, 486 F.2d 569, 576 (CCPA 1973).

Where there is "no indication that one skilled in the art would accept without question [the instant compounds and method of use] and no evidence has been presented to demonstrate that the claimed products do have those effects *Novak*, 306 F.2d at 928, an applicant has failed to sufficiently demonstrate sufficient utility and therefore cannot establish enablement."' *In re Rasmusson,* 75 USPQ2d 1297 (CAFC 2005). The claimed invention is not enabled without undue experimentation for the following reasons:

For rejection under 35 U.S.C. 112, first paragraph, the following factors must be considered. *In re Wands*, 8 USPQ2d 1400, 1404 (CAFC, 1988): "The factors to be considered [in making an enablement rejection] have been summarized as a) the breadth of the claims, b)

the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and, the quantity of experimentation necessary, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex prate Formal*, 230 USPQ 546. The breath of the claims includes all hydrocarbon groups. The compounds embraced by the claims are so numerous and are in the hundreds of thousands or millions, including solvates, polymorphs and metabolites. The nature of the invention is using the compounds as pharmaceuticals. The specification fails to disclose any nexus between the instant compounds and treating/preventing all respiratory, urinary and gastrointestinal (GI) diseases mediated by muscarinic receptors.

There is no known prior art that teaches applicability of similar compounds, solvates, polymorphs and metabolites thereof for treating/preventing all respiratory, urinary and gastrointestinal (GI) diseases mediated by muscarinic receptors. For example, see US 2,921,070. Different polymorphs of a specific compound usually have different crystalline structures due in part to "how" each crystal is made, and their solvates must have specific number of moles of water, while the metabolites must have substantial structural difference from the original compounds. The specification has not provided any evidence contrary to these accepted facts in the art. The specification fails to disclose the number of moles of water that would form the solvates, the crystalline structures of the polymorphs and how they are formed, and the structures of the metabolites and how they are formed in and/or outside the body. Also, the specification fails to disclose how a "normal" human predisposed to all of the listed diseases would be identified and the diseases prevented, or how one whose muscarinic receptors requires "mediation" could be identified so as to commence preventive intervention.

There is no absolute predictability or established correlation between the claims and the specification disclosures. The uncertainty presents one of ordinary skill in the art with obstacles and prevents her from accepting the invention on its face. Predictability in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. In the instant invention, there is no direction or guidance by applicant. There is no evidence in the specification that established correlation between the disclosure and the instantly claimed invention. *See Ex parte Mass*, 9 USPQ2d 1746, (1987).

It is quite possible that a mutation in the gene for the protein responsible for muscarinic receptors may lead to increased/decreased levels. To use the invention as claimed, one of ordinary skill in the art would have to perform experimentation in every instance to determine if the increase/decrease is due to genetic mutation in a patient or not. After prospective patients are identified and treated, assays must be performed on each one to determine if treatment is successful. However, the specification fails to disclose a routine procedure to perform such assay. Therefore, to make and use the instant invention, one of ordinary skill in the art would have to perform significant amount of experimentation. Such is deemed undue experiment under the US patent practice.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding any of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. By deleting prevention and limiting the diseases to those, which have support in the specification the rejection would be overcome.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. For the reasons set forth above under 35 USC 112, first paragraph the claims are indefinite.

The terms "solvates" "polymorphs", "metabolites" and "hydrocarbon group" are not defined in the claims so as to ascertain the metes and bounds of the claims. Therefore, they are indefinite. See the Examiner's suggestions above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10, are rejected under 35 U.S.C. 103(a) as being unpatentable over Itho et al., EP 0 108986 A1, in view of Sugara et al., J. Med. Chem. (2002), Vol. 45(4), pp. 984-987, and Takeuchi et al., EP 0 801 067 B1.

Applicant claims compounds of formula I, composition thereof and method of use for treating respiratory, urinary and gastrointestinal (GI) diseases mediated by muscarinic receptors.

Determination of the scope and content of the prior art (MPEP 2141.01)

Itho et al., teach similar compounds, their composition and method of use for treating dysuria (urinary disease). The compounds have pyridine as cationic nitrogen-containing cyclic ring. See the abstract, pages 2, 12-15.

Takeuchi et al., teach similar compounds, their composition and method of use as muscarinic receptors antagonist. The compounds have azobicyclic as cationic nitrogen-containing cyclic ring. See the abstract, pages 2-4.

Sugara et al., teach essential features of muscarinic receptors antagonists as comprising an aromatic cluster, a spacer, a cationic nitrogen-containing cyclic ring and an hydrophobic site close to the ring. The compounds have pyridine as cationic nitrogen-containing cyclic ring. See page 984, Design and Synthesis and figure 2.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

The difference between the instant invention and that of Itho et al., is that the cationic nitrogen-containing cyclic ring by applicant is azobicyclic (a bridged pyridine) instead of pyridine by Itho et al.

The difference between the instant invention and that of Takeuchi et al., is that the azobicyclic by applicant is a bridged pyridine (having a bond between 1,3-bridge) instead of C-2 bridged pyridine (a 1,4-bridge) by Takeuchi et al.

The difference between the instant invention and that of Sugara et al., is that the cationic nitrogen-containing cyclic ring by applicant is azobicyclic (a bridged pyridine) instead of pyridine by Sugara et al.

Finding of prima facie obviousness---rational and motivation (MPEP 2142.2413)

None of the prior arts disclosed the specific bridged pyridine in the instant compounds. However, under the recent decision in *KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct. 1727,-----, 82 USPQ2d 1385 (2007), obvious to try is now appropriate test of motivation.

When there is motivation

> To solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under [35 USC] 103.

A person of ordinary skill would have good reason to replace pyridine in the compounds of Itho et al., with a bridged pyridine. The limited and available options are 1) a pyridine with a bridge form by C-1 between 1,3-carbon atoms, 2) a pyridine with a bridge form by a bond between 1,3-carbon atoms, or 3) a pyridine with a bridge form by C-1 between 1,4-carbon atoms. These are identifiable and finite options. There is anticipated success because both bridged and non-bridged pyridines are successfully used by prior arts. Therefore, the instant invention is prima facie obvious from the teachings of Itho et al., Takeuchi et al., and Sugara et al.

Claims 11-12, 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugara et al., J. Med. Chem. (2002), Vol. 45(4), pp. 984-987.

Applicant claims a process of making compounds of formula I, comprising the condensation of formula III with formula IV to form compounds of formula V, removing the protecting group from formula V to form VI and alkylating formula VI to form compound of formula I. In preferred embodiments, the protecting group is benzyloxy and the solvent is methanol.

Determination of the scope and content of the prior art (MPEP 2141.01)

Sugara et al., teach similar process of making compounds of formula I. The protecting group is benzyloxy and the solvent is methanol. See scheme 3, steps (c) to (e) and column 2, page 985, last paragraph.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

The difference between the instant invention and that of Sugara et al., is that the starting reagents have different substituents and therefore, are analogous compounds.

Finding of prima facie obviousness---rational and motivation (MPEP 2142.2413)

However, the use of an analogous starting material in a well-known process is prima facie obvious. *In re Durden,* 226 USPQ 359, (1985). There is no evidence in the specification or the prior art that the substituents have any effect on the reaction process. Therefore, the instant invention is prima facie obvious from the teaching of Sugara et al. One of ordinary skill in the art would have known to change the substituents at the time the invention was made. The motivation is to avoid the prior art.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taofiq A. Solola, PhD. JD., whose telephone number is (571) 272-0709. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

TAOFIQ SOLOLA
PRIMARY EXAMINER

Group 1625

September 12, 2007